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Award Number: DAMD17-03-2-0028

TITLE: A Randomized Placebo-Controlled Trial of Citalopram for Anxiety Disorders
Following Traumatic Brain Injury

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REPORT DATE: April 2009

TYPE OF REPORT: FINAL

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188		
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1. REPORT DATE (DD-MM-YYYY) 04/30/2009		2. REPORT TYPE Final		3. DATES COVERED (From - To) 1 April 2003 – 31 March 2009	
4. TITLE AND SUBTITLE A Randomized Placebo-Controlled Trial of Citalopram for Anxiety Disorders Following Traumatic Brain Injury			5a. CONTRACT NUMBER DAMD17-03-2-0028		
6. AUTHOR(S) Michael S. Jaffe			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Henry M. Jackson Foundation for the Advancement of Military Medicine Rockville, MD 20852			8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick Maryland 21702-5012			10. SPONSOR/MONITOR'S ACRONYM(S) USAMRMC		
			11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The overarching goal of this project was to study the effects of a serotonin reuptake inhibitor (SRI), citalopram, for the treatment of anxiety experienced by individuals after traumatic brain injury (TBI). Specifically, this project sought to treat individuals who meet criteria for DSM-IV diagnosis of <i>Anxiety Disorder Due to a General Medical Condition</i> , within 3 to 24 months of TBI. A randomized placebo controlled design with 1-year follow-up was utilized to evaluate the effectiveness of citalopram in alleviating significant anxiety symptoms that cause significant distress and can lead to medical retirement of active duty soldiers. 19 participants (8 Citalopram and 11 placebo) completed the study. The study did not find significant differences in the anxiety measures between the Citalopram and placebo groups at the week 12 assessment. However, the Citalopram group had lower scores [STAI and HAM-A] than the placebo group. The lack of statistical significance may have been due in part to the small sample size. The small sample size resulted from difficulties identifying service members who were able to participate in this study as a result of war injuries from OIF/OEF.					
15. SUBJECT TERMS Traumatic Brain Injury; Anxiety Disorders; SRI Treatment; Randomized Controlled Trial					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 9	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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Introduction:

The overarching goal of this project was to determine the effectiveness of Citalopram for the treatment of anxiety disorders following traumatic brain injury (TBI) and examine the possible longer term effectiveness of treatment with Citalopram on symptom reporting and return to work/ duty.

The hypothesis: participants receiving a 12 week course of Citalopram will report fewer and less severe anxiety symptoms than those receiving a 12 week course of placebo.

Body:

Participants who experienced a traumatic brain injury [TBI] 3 to 24 months ago and were experiencing anxiety were eligible for the study. If they agreed to participate, they signed informed consent prior to research testing. An informational script about the study was read to individuals. After the script was read, the individual was given the informed consent to review. Individuals were ineligible to participate in the study until they reached a Rancho Los Amigos level of 7 or 8. If there were any concerns as to capacity to consent, the neuropsychologist and/or psychiatrist involved in the study assessed the individual level of comprehension prior to consent. Any confusional state prohibited an individual from being at a 7 or 8 Rancho level. After signing the informed consent, tests and scales were administered and participants were randomized to receive a 12 week course of Citalopram or placebo. Female participants of childbearing potential were given a serum pregnancy test prior to randomization. If the test was positive, she was ineligible to participate in the study.

Eligible, consented participants received an increasing dose of Citalopram, up to 40 mg, or placebo, up to 4 pills over the course of the 12 weeks. A blood sample was drawn after completion of the 12 week treatment period. This was used to obtain Citalopram blood levels as a measure of compliance. A two- week taper followed the treatment period. Study participants received comprehensive multidisciplinary evaluations at a DVBC site, including neuropsychological and psychiatric interviews at baseline, 12 weeks and 12 months.

Since the last annual report [April 2008], there have been no modifications to the protocol. There have not been any enrollments since 2007. The total number of subjects enrolled over the entire study length is 19.

The primary outcome measures for this study were the DSM-IV diagnostic criteria for Anxiety Disorder Due to General Medical Condition – both “caseness” and number of generalized anxiety symptoms [GAD] symptoms, and the total score on the Spielberger State Anxiety Inventory [STAI] and the overall score from the Hamilton Anxiety Rating Scale [HAM-A].

Meeting the criteria for having an anxiety disorder was determined through an algorithm using the Hamilton Anxiety Scale. Of the 19 subjects evaluated at baseline, 17 met the DSM-IV criteria of Anxiety Disorder Due to a General Medical Condition using the Hamilton Anxiety Scale algorithm. The remaining two subjects met criteria through the use of the Structured Clinical Interview for DSM Disorders (SCID). Determination for diagnosis was completed by the Principal Investigator, psychiatrist, physician assistant, or nurse. Of the 15 subjects evaluated at the Week 12 evaluation, 11 met the criteria for an anxiety disorder using the Hamilton Anxiety Scale algorithm. Of the remaining four, two met criteria through the use of the SCID, and two did not meet criteria for the disorder.

The Spielberger State Anxiety Inventory consists of 20 items that ask how a person feels now, and reflects situational factors that may influence anxiety levels. Scores range from 20-80 and the higher the score the greater the level of anxiety.

Key Research Accomplishments:

All available data was entered into an electronic data capture system. Student’s T- tests were used to compare the mean scores of the two study groups. Dr. Karen Schwab presented the interim data of this study at the National DVBIC Investigators meeting September 2007. At this meeting, site PIs as well as the study PIs and coordinators agreed the study was important but saw no feasible way to recruit patients into the study under current wartime conditions. The main site for accrual was WRAMC and given the lack of any statistical efficacy or trend to efficacy for the use of citalopram they too felt continuation was futile.

Reportable Outcomes:

All enrolled subjects were male on active duty. They were primarily Caucasian (84.2%), in the United States Army (57.9%) and single (52.6%). At the time of baseline evaluation, the

mean age of the subjects was 26.9 years (range 20-41 years). The mean number of years of education in the sample was 12.9 years (range 11-18 years). For subjects who completed both a baseline and 12 week evaluation, the mean total score at baseline on the Spielberger State Anxiety Inventory was 42.7. The mean total score for the same group at the 12 week evaluation was 42.3.

Eight participants were randomly selected to receive a 12-week course of Citalopram and 11 were randomly selected to receive a 12 week course of placebo. Participants received an increasing dose of Citalopram (up to 40 mg) or placebo (up to 4 tablets) over the 12 week period.

Results

At baseline, 19 participants (8 Citalopram and 11 placebo) completed the STAI and 18 (8 Citalopram and 10 placebo) completed the HAM-A. Four subjects who completed the baseline assessment did not complete the week-12 assessment. The mean scores on the STAI for the Citalopram and placebo groups were similar at baseline but at week 12, the mean score for the Citalopram group was lower than for the placebo group (Table 1). The mean scores on the HAM-A were lower for the Citalopram group than for the placebo group at baseline and at week-12. However, none of the differences on either anxiety measure were statistically significant.

Discussion

This study did not find any significant differences in anxiety measures between the Citalopram and placebo groups at the week-12 assessment. However, the Citalopram group had lower scores on both the STAI and the HAM-A at week-12 than the placebo group. The lack of statistical significance may have been due in part to the small sample size, which is the study's major weakness. The planned sample size was 104, 52 to receive Citalopram and 52 to receive placebo. The small sample size resulted from difficulties identifying service members who were able or willing to discontinue taking other psychotropic medications, which was required in order to participate. The study was designed during peacetime. With the occurrence of conflicts in Afghanistan and Iraq beginning, recruitment began while the wars in Iraq and Afghanistan were underway and many service members who returned from those locations were being treated for psychological conditions and multiple physical injuries on medication that requiring discontinuance in order to participate in the study.

Assessment	Citalopram Mean (SD) [n]	Placebo Mean (SD) [n]	p-value
<i>State-Trait Anxiety Index</i>			
Baseline (for all participants)	43.1 (13.9) [8]	43.0 (19.3) [11]	0.988
Baseline (only for those who completed week-12 assessment)	42.3 (14.3) [6]	42.9 (21.6) [9]	0.957
Week 12	37.2 (13.4) [6]	45.7 (18.3) [9]	0.349
<i>Hamilton Anxiety Rating Scale</i>			
Baseline (for all participants)	18.5 (9.1) [8]	19.6 (10.7) [10]	0.820
Baseline (only for those who completed week-12 assessment)	16.8 (9.5) [6]	19.0 (10.8) [8]	0.703
Week 12	10.8 (10.9) [6]	17.6 (12.7) [8]	0.313

Table 1

Comparison of Anxiety Measures at Baseline and Week-12 Assessments by Study Group

Conclusions:

In 2003, this multisite study was implemented in seven DVBIC network sites: MTF's: WRAMC, NMSD, Wilford Hall AFB; VA's: Palo Alto, Richmond, Tampa and MN. A total of 19 subjects were enrolled from all sites between 2003-2007. The last subject enrolled in April 2007 with the 12 month follow-up occurring in April 2008.

There were challenges in patient accrual particularly with the start of OEF and OIF with the exigencies of war reducing the available patient pool and eligibility. Despite taking multiple steps {monthly research co-coordinator calls, extension of eligibility 3-24 month to permit

more acutely injured patients into the study and letter of appreciation to subjects} to increase the recruitment and enrollment, the number of patients eligible at the time of screening was negligible.

Difficulties encountered: 1) time intensive study - weekly calls [and/or visits] and multiple forms to complete; 2) patient population - many did not meet full criteria/ already taking an SSRI especially since the commencement of OEF and OIF; 3) reluctance of patient physicians to allow patients to be taken off current regime of medications and/or other medications which were contraindicated to the study drug; and 4) some patients never achieved the appropriate Rancho level.

Patient enrollment closed at sites by January 2008. The reason for trial closure was secondary to the poor accrual in the trial that could not justify the continued use of taxpayer dollars.

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